09/716,054
Updated Search
Lycock 7/14/06

```
d his

     (FILE 'HOME' ENTERED AT 19:31:56 ON 14 JUL 2006)

     FILE 'BIOSIS, CAPLUS, EMBASE, MEDLINE, JAPIO' ENTERED AT 19:32:15 ON 14
     JUL 2006
L1             6 S SLFPYEEI
L2             2 DUPLICATE REMOVE L1 (4 DUPLICATES REMOVED)

=>
```

ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
AN 2000:802773 CAPLUS
DN 134:125901
ED Entered STN: 15 Nov 2000
TI Mechanistic studies of affinity modulation
AU Rosen, Michael K.; Amos, Christopher D.; Wandless, Thomas J.
CS Department of Chemistry, Stanford University, Stanford, CA, 94305, USA
SO Journal of the American Chemical Society (2000), 122(48), 11979-11982
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
CC 1-12 (Pharmacology)
Section cross-reference(s): 6
AB A synthetic ligand for the protein FKBP12 was covalently linked to a peptide ligand (pYEEI) for the Fyn SH2 protein to create a bifunctional mol. called SLFpYEEI. This bifunctional mol. can simultaneously bind both proteins to form a trimeric complex. When SLFpYEEI is precomplexed with FKBP12, the peptide ligand binds 6-fold more weakly to the Fyn SH2 domain than SLFpYEEI alone. Isotope-edited NMR spectroscopy was used to investigate the mol. basis for the observed reduction in affinity. The results suggest that interactions between the pYEEI peptide and FKBP12 may play a significant role in diminishing the affinity of SLFpYEEI for the Fyn SH2 domain.
ST FKBP12 peptide ligand protein drug design
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FKBP-12 (FK 506-binding protein, 12,000-mol.-weight); mechanistic studies of affinity modulation)
IT Protein motifs
(SH2 domain; mechanistic studies of affinity modulation)
IT Drug design
(mechanistic studies of affinity modulation)
IT 225108-46-3
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(mechanistic studies of affinity modulation)
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Amzel, L; Current Opin Biotechnol y 1998, V9, P366 CAPLUS
(2) Atwell, S; Science 1997, V278, P1125 CAPLUS
(3) Briesewitz, R; Proc Natl Acad Sci U S A 1999, V96, P1953 CAPLUS
(4) Carson, M; J Appl Crystallogr 1991, V24, P958
(5) Cohen, G; Cell 1995, V80, P237 CAPLUS
(6) Delaglio, F; J Biomol NMR 1995, V6, P277 CAPLUS
(7) Delano, W; Science 2000, V287, P1279 CAPLUS
(8) Holt, D; J Am Chem Soc 1993, V115, P9925 CAPLUS
(9) Johnson, B; J Biomol NMR 1994, V4, P603 CAPLUS
(10) Kay, L; J Am Chem Soc 1992, V114, P10663 CAPLUS
(11) Kay, L; J Magn Reson Ser A 1994, V109, P129 CAPLUS
(12) Meadows, R; Biochemistry 1993, V32, P754 CAPLUS
(13) Michnick, S; Science 1991, V252, P836 CAPLUS
(14) Mulhern, T; Structure 1997, V5, P1313 CAPLUS
(15) Pawson, T; Genes Develop 2000, V14, P1027 CAPLUS
(16) Pawson, T; Nature 1995, V373, P573 CAPLUS
(17) Rajagopal, P; Protein Sci 1997, V6, P2624 CAPLUS
(18) Rosen, M; Biochemistry 1991, V30, P4774 CAPLUS
(19) Sheinerman, F; Current Opin Struct Biol 2000, V10, P153 CAPLUS
(20) Smithgall, T; J Pharmacol Toxicol Methods 1995, V34, P125 CAPLUS
(21) Xu, R; Biopolymers 1993, V33, P535 CAPLUS
(22) Zhang, O; J Biomol NMR 1994, V4, P845 CAPLUS

ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
DUPLICATE 1
AN 2004:465119 BIOSIS
DN PREV200400460986
TI Quantitative analyses of bifunctional molecules.
AU Braun, Patrick D.; Wandless, Thomas J. [Reprint Author]
CS Dept Mol Pharmacol, Stanford Univ, Stanford, CA, 94305, USA
wandless@stanford.edu
SO Biochemistry, (May 11 2004) Vol. 43, No. 18, pp. 5406-5413. print.
ISSN: 0006-2960 (ISSN print).
DT Article
LA English
ED Entered STN: 1 Dec 2004
Last Updated on STN: 1 Dec 2004
AB Small molecules can be discovered or engineered to bind tightly to biologically relevant proteins, and these molecules have proven to be powerful tools for both basic research and therapeutic applications. In many cases, detailed biophysical analyses of the intermolecular binding events are essential for improving the activity of the small molecules. These interactions can often be characterized as straightforward bimolecular binding events, and a variety of experimental and analytical techniques have been developed and refined to facilitate these analyses. Several investigators have recently synthesized heterodimeric molecules that are designed to bind simultaneously with two different proteins to form ternary complexes. These heterodimeric molecules often display compelling biological activity; however, they are difficult to characterize. The bimolecular interaction between one protein and the heterodimeric ligand (primary dissociation constant) can be determined by a number of methods. However, the interaction between that protein-ligand complex and the second protein (secondary dissociation constant) is more difficult to measure due to the noncovalent nature of the original protein-ligand complex. Consequently, these heterodimeric compounds are often characterized in terms of their activity, which is an experimentally dependent metric. We have developed a general quantitative mathematical model that can be used to measure both the primary (protein + ligand) and secondary (protein-ligand + protein) dissociation constants for heterodimeric small molecules. These values are largely independent of the experimental technique used and furthermore provide a direct measure of the thermodynamic stability of the ternary complexes that are formed. Fluorescence polarization and this model were used to characterize the heterodimeric molecule, SLFpYEEI, which binds to both FKBP12 and the Fyn SH2 domain, demonstrating that the model is useful for both predictive as well as ex post facto analytical applications.
CC Mathematical biology and statistical methods 04500
Biochemistry studies - General 10060
Biophysics - Biocybernetics 10515
IT Major Concepts
Biochemistry and Molecular Biophysics; Methods and Techniques; Models and Simulations (Computational Biology)
IT Chemicals & Biochemicals
FKBP12; Fyn: SH2 domain; SLFpYEEI: heterodimeric molecule; protein-ligand complex; ternary complex
IT Methods & Equipment
biophysical analysis: laboratory techniques; fluorescence polarization: laboratory techniques, spectrum analysis techniques; quantitative analysis: mathematical and computer techniques; quantitative mathematical model: laboratory equipment
IT Miscellaneous Descriptors
intermolecular binding; thermodynamic stability